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HUMAN SUBJECT PARTICIPATION IN RESEARCH PROJECTS: ETHICAL CONSIDERATIONS (WITH EMPHASIS ON PROCEDURES CONDUCTED AT DRDC TORONTO)

by Dr. Jack P. Landolt

The principle of medical and surgical morality, therefore, consists in never performing on man an experiment which might be harmful to him to any extent, even though the result might be highly advantageous to science, i.e., to the health of others.[1]

Claude Bernard, French Physiologist, 1865

Every human being of adult years and sound mind has the right to determine what shall be done with his body.[2]

Justice Cardozo, American Judge, 1914

The subject of medical experimentation is entitled to a full and frank disclosure of all of the facts, probabilities and opinions which a reasonable man might be expected to consider before giving his consent.[3]

Justice Emmett Hall, Canadian Judge, 1965

The modern foundations for the ethical principles of human research have their origin in the response of the international community to the barbarism of the Nazi medical experiments,[4] which led to the promulgation of the Nuremberg Code.[5] Other subsequent abuses and breaches in conduct by prominent research organizations towards subjects participating in research subsequently led to the Declaration of Helsinki[6] and other institutional guidelines for the ethical conduct of research employing human subjects. Of significance here are the Tuskegee syphilis experiments (1932-1972)[7] and the Willowbrook hepatitis study (1950s-1960s),[8] the abuses of which had a profound influence on the United States in issuing their set of research ethics guidelines, the so-called Belmont Report.[9] More recently, the deaths of Jesse Gelsinger (1999)[10] and Ellen Roche (2001)[11] in approved medical experiments have placed the focus in the United States on the medico-legal adequacy of the institutional

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104-01222/

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Research Ethics Boards (REBs) in fulfilling their mandate. In Canada, legal actions that favoured the plaintiffs following breaches in research are best exemplified by the disastrous drug studies conducted in the Walter Halushka (1965)[12] and Julius Weiss (1982)[13] cases. These and other instances of research misconduct in Canada subsequently led to the issuance of the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans,[14] and acceptance of the international set of guidelines, International Conference on Harmonization Good Clinical Practice (ICH GCP).[15]

"The essence of voluntary, informed consent is a full discussion of the nature of the study between a scientifically competent person and the prospective subject."

All of the breaches cited in the above and other instances where contravening good ethical research practices has occurred may be grouped into the following two major categories:

a. Breaches in science, above all else for personal and institutional gain:

- falsifying data;
- breaching privacy without consent, e.g., third party rights;
- interference from the sponsor;
- failure to get institutional Research Ethics Board (REB) approval;
- conflict of interest; and
- failure to get federal government approval.

a. Breaches in lack of regard for research participants' rights:

- done without subject's knowledge;
- done without subject's consent;
- continuation of study, even when adequate treatment has been established;
- done even when it is known that treatment does not work;
- changing inclusion criteria to fit subject's characteristics;
- adverse effects not adequately specified;
- incompetent institutional REB appointed;
- prior animal testing not conducted;
- improper use of disadvantaged or naïve individuals as subjects (e.g., prisoners of war, inmates, poor labourers, impressionistic young adults, children, mentally-challenged individuals, etc.); and
- subjects not told of financial or other interests.

ETHICAL CONSIDERATIONS AT DEFENCE R&D CANADA – TORONTO

DRDC Toronto is Canada's centre of expertise for defence research and development in human performance and protection, human-system integration and operational medicine. Its mission is to employ research and development to enhance the effectiveness, and ensure the health and safety, of the human in any human-machine system or adverse environment. In accomplishing this mandate, experiments utilizing human subjects are often essential. Furthermore, it is mandatory at DRDC Toronto that all research projects, where there is human-subject participation, will be conducted in a manner that will afford maximal protection to the subject, and that the experimental design is sound and permits maximal utilization of the results. That is, the collection of data must be sufficiently important to warrant exposing the subject to the experimental methods. This implies that the best ethical practices must be employed to achieve the highest ethical standards in conducting research involving human subjects. To meet these standards, the laboratory head, commanding officer, scientific and technical programme managers, project directors, contractors, investigators, technologists and the institutional research-ethics committee all have commitments and obligations, both moral and legal, in the proper use of humans as research subjects.

The DRDC Toronto Human Research Ethics Committee (HREC) was formed in 1979 to assure human subjects that experimental research involving them would be done properly and safely, and that it would also respect their individual rights. DRDC Toronto has now developed a new set of guidelines[16] for use by the HREC for the ethical conduct and

treatment of human subjects in research that are based on current nationally and internationally accepted practices. Most significantly, the key practices employed by the DRDC Toronto HREC in this regard were implemented from the Nuremberg Code, the Helsinki Declaration, the Belmont Report, the Tri-Council Policy Statement, and Department of National Defence Administrative Orders and Directives (DAODs).[17]

The protection of the rights of human research subjects is the embodiment of the Nuremberg Code, which was formulated to guard against any repeat of the medical research atrocities committed during the Second World War. The Nuremberg Code requires that researchers must design experiments that protect the well being of their subjects; it also declares that subjects have the right to protect themselves. That is, subjects have the absolute right to exercise freedom of choice on whether to participate in an experiment by giving informed consent, and the right also to withdraw at any time from an experiment without suffering any subsequent consequences.

An important follow-on to the Nuremberg Code is the various revisions of the ethical principles that make up the Helsinki Declaration. Although the focus of the Nuremberg Code is primarily on the rights of the research subject, the subsequent recommendations of the Helsinki Declaration place the onus for ethical conduct on the obligations of the researcher to the research subject. A key tenet of a recent revision of the Helsinki Declaration is the need for prior peer review of a research protocol, by an appointed committee independent of the investigator, regarding the design and performance of any experimental procedures involving human subjects.

Both the Nuremberg Code and the Helsinki Declaration are being used worldwide as models in promulgating institutional guidelines for the proper conduct of experimental research involving human subjects. An important document that embodies the ethical practices of these two guidelines is the Belmont Report, which was issued by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. This document identifies the ethical principles of respect for persons, beneficence and justice as particularly relevant to human-subject research.

The Tri-Council Policy Statement cited above was issued jointly in 1998 by the Medical Research Council of Canada,[18] the Natural Sciences and Engineering Research Council of Canada and the Social Sciences and Humanities Research Council of Canada. It offers a further set of ethical principles that incorporate those of the Belmont Report. As extracted from the Tri-Council Policy Statement (and modified, as appropriate, to meet DRDC Toronto conditions), this set of principles addresses:

- **Respect for Human Dignity:** protecting the multifaceted interests of the subject, i.e., the bodily, psychological and cultural interests.
- **Respect for Free and Informed Consent:** respecting the exercise of informed consent, which involves dialogue, process, rights, duties and requirements for subject consent.
- **Respect for Vulnerable Persons:** providing care and special protection against abuse, exploitation or discrimination.
- **Respect for Privacy and Confidentiality:** protecting the access, control and dissemination of personal subject information to avoid mental or psychological anguish.
- **Respect for Justice and Inclusiveness:** being fair in reviewing research protocols, and not unfairly burdening anyone as a research subject in respect to harm, or discriminating against any subject who could benefit from the research on the basis of gender, culture, etc.
- **Balancing Harms and Benefits:** establishing that the foreseeable harms to the subject do not outweigh the anticipated benefits of the research.
- **Minimizing Harm:** employing methods for assuring subjects that risk of harm is minimized, including the employment of the smallest number of subjects and tests, minimal time involvement, and acceptable experimental design and data analysis to achieve scientific validity.
- **Maximizing Benefits (Beneficence):** establishing that the research benefits the subject, the Canadian Forces (CF) and society as a whole.

The purpose of the Tri-Council Policy Statement is to harmonize the ethics-review process in Canada to ensure that there is consistency in the ethical conduct of research involving human subjects. The Department of National Defence (DND) has directed the DRDC Toronto HREC to conduct its research-review proceedings in accordance with the Tri-Council Policy Statement in two DAODs. These

"The best ethical practices must be employed to achieve the highest ethical standards in conducting research involving human subjects."

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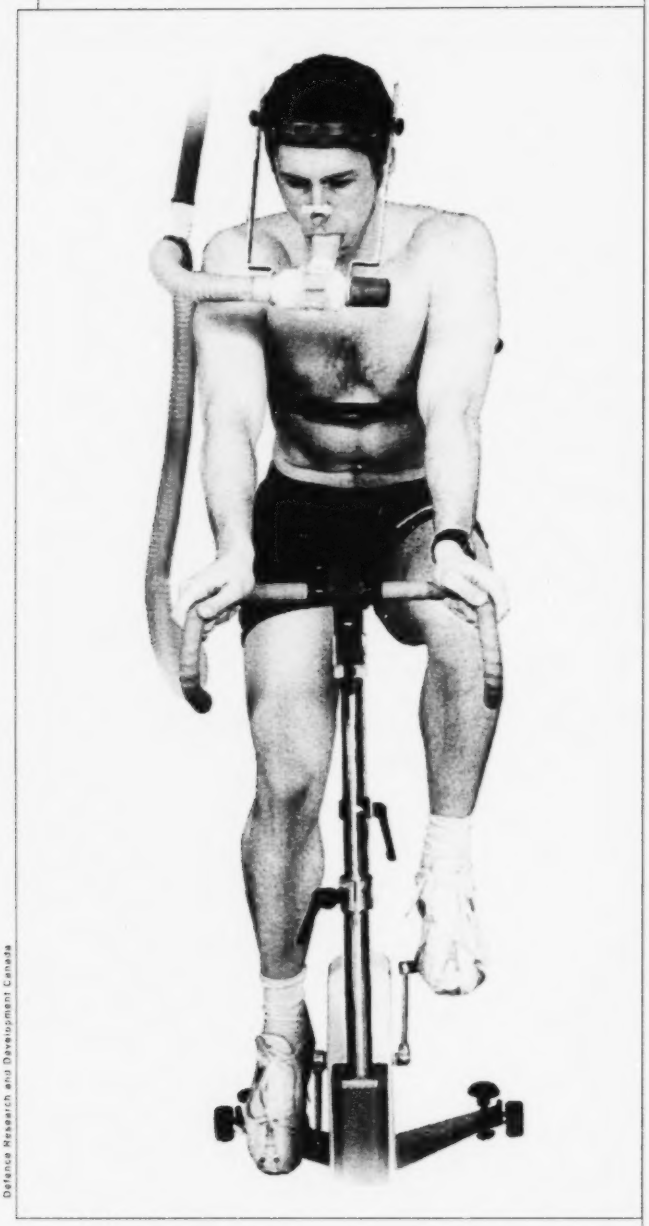

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DAODs set out the policy and approved administrative procedures regarding the use of human subjects in research protocols that the DRDC Toronto HREC reviews.

Concerning drug trials involving human subjects, DRDC Toronto complies with the dictates of the ICH GCP guidelines.

DRDC TORONTO HUMAN RESEARCH ETHICS COMMITTEE (HREC): COMPOSITION, MANDATE AND SCOPE

The DRDC Toronto HREC consists of the following committee members:

Chair: senior defence scientist from DRDC Toronto;
Monitoring Member: senior scientist or physician from the research community who is not an employee of DRDC Toronto;
Medical Member: medical officer or physician from DRDC Toronto;
Physiology Member: experienced physiologist from DRDC Toronto;
Psychology Member: experienced psychologist or behavioural scientist from DRDC Toronto;
Internal Lay Member: staff member from DRDC Toronto who is neither a scientist nor a physician;
External Lay Member: community member not affiliated with DRDC Toronto;
Member Knowledgeable in Law: community member knowledgeable in the applicable law; and
Member Knowledgeable in Ethics: knowledgeable person on ethical issues and options.

The Monitoring Member acts as an independent advisor not having any conflict of interest in the research projects. The Monitoring Member attends all meetings and monitors all Committee decisions, reporting any issues of concern directly to DRDC Toronto senior management. The Lay Members assist the Committee in interpreting potential subject attitudes or reactions to the research protocol, and advise on the clarity of instruction and informed consent details. The Member Knowledgeable in Law alerts and advises the HREC on legal issues and their implications, but does not provide formal legal opinions nor serve as legal counsel for the Committee. The Member Knowledgeable in Ethics alerts and advises the HREC on potential ethical issues and options.

The DRDC Toronto HREC provides a full or expedited review[19] of all protocols submitted to it, in which human subjects participate in research projects, to ensure that all policies, considerations, standards and safeguards as described or intended by the HREC guidelines[20] are appropriately applied. HREC approval must be obtained before resources are committed to a research project and before commencing with experimentation or preliminary testing.

A protocol review by the DRDC Toronto HREC determines whether or not:

- the risks to the subject are so outweighed by the sum of the benefits to the subject and the importance of the knowledge to be gained as to warrant a decision to allow the subject to accept the risks;
- the rights and welfare of the subject are adequately protected; and
- informed consent is obtained by adequate and appropriate methods in accordance with the provisions of the HREC guidelines.

Risk is defined as the possibility of harm or discomfort (physical, physiological, psychological, sociological or financial) as a consequence of any act or the omission of an act on an individual in a research project. Risk has two components: the probability of harm (i.e., whether frequent, likely, occasional, seldom, unlikely or impossible) and the severity of the harm (i.e., catastrophic, critical, marginal or negligible). Research investigators must address both of these aspects when writing a research protocol.

Free and informed consent is required at DRDC Toronto for all research projects involving experimentation of human subjects. The essence of voluntary, informed consent is a full discussion of the nature of the study between a scientifically competent person and the prospective subject. Therefore, the information that the subjects will be given before they agree to become participants in a research project needs to be identified. At a minimum, this includes a copy of the HREC-approved protocol for prospective subjects, which must include a voluntary consent form for signed consent or a covering letter for unsigned consent.[21] A research protocol employing either consent process must provide a full understanding of the research project's rationale, procedures, risks, benefits, expected outcomes, measures to ensure a human subject's safety and confidentiality, any expected follow-up studies, data usage, anticipated time commitment, remuneration and the intended disclosure. Subjects are instructed to read all of this information thoroughly, and are given every opportunity to adequately discuss and contemplate their participation in the research project before making any decision on whether or not to sign a consent form, or participate in a survey where there is a requirement for unsigned consent.

The DRDC Toronto HREC will review protocols involving the participation of human subjects in:

- all research projects developed by DRDC Toronto investigators and conducted at DRDC Toronto;
- naturalistic observations[22] conducted by DRDC Toronto investigators where informed consent is to be obtained;
- contract work (both research or testing) conducted at DRDC Toronto;
- DRDC Toronto contract work conducted off-site where the contractor has no access to an HREC;
- testing of equipment and protective ensembles by DRDC Toronto investigators to gather new facts;
- university-thesis research conducted at DRDC Toronto;
- instances where DRDC Toronto investigators are active participants in research projects at other institutions or units;
- instances where DRDC Toronto equipment employed in research projects at other institutions or units has the potential to cause harm;
- instances where DRDC Toronto employees have been given permission by DRDC Toronto management to act as subjects in DND-supported research projects with other institutions or units, including the Internet; or
- research projects conducted at other laboratories or units in DND that are submitted to the DRDC Toronto HREC for review.

Accordingly, investigators must prepare a research protocol for HREC review for any research project in which a research team:

- administers a biological or non-biological substance, takes a blood sample or removes other biological tissue, evaluates equipment and clothing to assess environmental effects, or performs any procedure, clinical, therapeutic or otherwise, upon the human subject for research rather than treatment;
- conducts experiments to collect data on an individual's behaviour or to obtain responses to an imposed stress or experimental situation, either directly or indirectly;[23]
- for the purpose of research (not administration), asks individuals personal questions or for opinions in a survey by telephone, e-mail, Internet, letter, questionnaire, interview, etc.; or
- for the purpose of research, uses non-public records and papers which contain private or confidential identifying information about any individual.

SUMMARY

Breaches in the conduct of research involving human subjects have led to a progression of corrective, institutional research ethics guidelines that include the Nuremberg Code, the Helsinki Declaration, the Belmont Report and, in Canada, the Tri-Council Policy Statement. DRDC Toronto has recently issued a set of research ethics guidelines that incorporates the relevant features of each of these models. The DRDC Toronto HREC reviews protocols submitted to it according to these guidelines, with particular attention paid to the risks and benefits to the subject involved in the research, and ensures that the rights and welfare of the subject are adequately protected, and that informed consent is obtained by adequate and approved means.

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NOTES

1. Cited in: David J. Rothman, "Were Tuskegee & Willowbrook 'Studies in Nature'?", *The Hastings Center Report*, 12 (2), pp. 5-7, 1982.
2. Cited in: David T. Marshall, "Consent in Medical Practice and Research," presentation at National Defence Medical Centre, Ottawa, Canada, November 29, 1991.
3. Cited in Marshall, *ibid.*
4. Nazi physicians and scientists conducted forced experiments on 'prisoners', including: mass sterilization, genetic engineering, deliberately infecting wounds, inducing gangrene and malaria, testing responses to untested drugs, and testing responses to human endurance (e.g., freezing temperatures and altitude decompression). See: David T. Marshall, *The Law of Human Experimentation*. Toronto: Butterworths Canada, pp. 3-10, for further information. The DVD video, Science and the Swastika, Channel 4 International, American Home Treasures, Division of BFS Entertainment & Multimedia Ltd., Richmond Hill, Ontario, Canada, 2001, provides detailed newsreel footage of many of these atrocities (for further details, see Web Site http://www.bfsent.com/).
5. The Nuremberg Code – see: Evelyne Shuster, "Fifty Years Later: The Significance of the Nuremberg Code," *The New England Journal of Medicine*, 337, pp. 1436-1440, 1997; also see Marshall, Note 4., pp. 123-124 (Appendix A).
6. World Medical Association (WMA) Declaration of Helsinki – "Ethical Principles for Medical Research Involving Human Subjects", October 2000 amendment. See Web Site http://www.wma.net/e/policy/17-c_e.html
7. Tuskegee Experiments - US Government study commencing in the 1930's on poor, syphilitic, black labourers who were denied treatment so that physicians could study the course of the disease. Subjects were told they had "bad blood", not syphilis. These experiments continued even when it became known that penicillin would treat the condition. The experiments stopped only when the *Washington Star* broke the story in 1972. This study never produced any substantial findings. See Rothman, Note 1.; Marshall, Note 4., pp. 10-15 for further information.
8. Willowbrook Study – Institutionalized, mentally challenged children were deliberately infected with hepatitis virus. Consent forms that parents signed were made to read as though the children would receive a vaccine rather than the virus. The rationale behind this approach was that these children would acquire this infection anyway; by participating in the study, they would receive better care. No consideration was given to addressing the societal conditions that fostered the hepatitis virus. This is an example of bad science; critical breakthroughs in hepatitis virus control occurred elsewhere. See Rothman, Note 1. for further information
9. The Belmont Report: "Ethical Principles and Guidelines for the Protection of Human Subjects of Research," The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, Washington, D.C., 1979 (1998 update). Also see Marshall, Note 4., pp. 125-137 (Appendix B)
10. Jesse Gelsinger was diagnosed with a mild, well-controlled hereditary liver disease. He volunteered in a gene therapy trial conducted at the University of Pennsylvania. He did not fit the inclusion criteria, which were then changed to include him. No notification was made to the Food and Drug Administration (FDA), the US drug regulatory agency, of these changes. No mention was made to Mr. Gelsinger of prior deaths or adverse effects. The researchers had a financial stake in the study. Jesse Gelsinger died of multi-organ failure at eighteen years of age, four days after receiving the drug through two catheters placed into his groin. His death has led to renewed efforts by the FDA to implement an accredited human-subject protection program. See Colleen Clements, "Clinical research: Nothing ventured, nothing gained," *The Medical Post*, 36(21), September 19, 2000; Celia Milne, "Trials and tribulations," *The Globe and Mail*, p. R5, July 10 2001 for further information.
11. Ellen Roche volunteered for a Johns Hopkins University study aimed at understanding asthma better. The objective was to inhale the chemical hexamethonium to study a bronchial-wall (airway) nerve response. She was never told that this chemical had not been used as a treatment for decades and was never used as an inhalant. She could not inhale without coughing. Severe lung congestion occurred, followed by death from slow asphyxiation one month later at age twenty-four. Johns Hopkins suspended research and conducted an investigation which concluded that the study should not have received REB approval. The FDA suspended all federally funded research at Johns Hopkins, lifting the suspension only when substantial redrafting of guidelines and revision of the ethics procedures had taken place. See Colleen Clements, "Researching research," *The Medical Post*, 37(31): September 18 2001; Sarah Ramsay, "Johns Hopkins takes responsibility for volunteer's death," *The Lancet*, 358: p. 213, 2001; Andrew Mills, "Human testing alarm raised," *National Post*, p. A13, July 30, 2001 for further information.
12. Walter Halushka was a student volunteer in an anesthesia (drug) study at the University of Saskatchewan that included cardiac catheterization. He did not consent to the catheterization nor was he told that the drug was a new one. He suffered a cardiac arrest and required an open-chest massage. The University was found negligent by the Saskatchewan Court of Appeal for failing to adequately disclose all of the details of the experimental procedure. See *Halushka v. University of Saskatchewan* [1965], 53 D.L.R. (2d) 436 (Sask. C.A.); Kathleen Cranley Glass and Benjamin Freedman, "Legal liability for injury to research subjects," *Clinical and Investigative Medicine*, 14(2): pp. 176-180, 1991; Marshall, Note 4., pp. 16-18 for further information.
13. Julius Weiss, a Montreal hospital heart patient, was recruited as a subject by his physician in a clinical trial assessing the ability of indomethacin (eye) drops to reduce retinal swelling. The drug effects were assessed by way of a fluorescien angiogram. The institutional REB approved the study. He was told that the risks would be minor; no mention was made of two earlier deaths from acute reactions to the fluorescien dye. Mr. Weiss, aged sixty-two years, died almost immediately after receiving the fluorescien dye injection. His family successfully sued the REB and the hospital. Among other things, the judgement that was rendered stipulated that the REB failed to emphasize the risks of the procedure on the consent form. See *Weiss v. Solomon* [1989], 48 C.C.L.T. 280 (Que. S.C.); Glass and Freedman, Note 12.; Marshall, Note 4., pp. 17-18 for further information.
14. Tri-Council Policy Statement: "Ethical Conduct for Research Involving Humans," National Council on Ethics in Human Research, Ottawa, 1998. Also see Marshall, Note 4., pp. 148-221 (Appendix F). Web Site http://www.nserc.ca/programs/ethics/english/index.html
15. "Good Clinical Practice: Consolidated Guideline," ICH Harmonized Tripartite Guideline, Health Canada, 1997. Web Site www.hc-sc.gc.ca/hpb-dgps/therapeut
16. "Guidelines for Human Subject Participation in Research Projects," Defence R&D Canada – Toronto, 1 April 2002 (Web Site http://www.toronto.drdc-rddc.gc.ca). These guidelines represent a major revision of an earlier set of guidelines that were produced in 1979 when DRDC Toronto was Defence & Civil Institute of Environmental Medicine (DCIEM). DCIEM became DRDC Toronto on 1 April 2002.
17. DAOD 5061-0: "Research Involving Human Subjects," and DAOD 5061-1: "Research Involving Human Subjects – Approved Procedures," Director of Health Operations, Director General Health Services, Department of National Defence, Ottawa, 1998.
18. Now called Canadian Institutes of Health Research.
19. An expedited review is conducted in most instances of minimal risk, i.e., when the possibility of harm or discomfort occurring in a research project is anticipated to be no greater than that ordinarily encountered by the research subject in daily life or during the performance of routine physical or psychological examinations or tests. It is also conducted when there are minor modifications made to a previously approved submission. A full review is conducted in all instances of acceptable risk, i.e., when the possibility of harm occurring in a research project is anticipated to be greater than that ordinarily encountered by the research subject in daily life or during routine examinations or tests. A full review is the default condition for all research involving human subjects, and is conducted by the full DRDC Toronto HREC. An expedited review is conducted by the Chair, HREC and at least one other Committee Member. The DRDC Toronto HREC will not approve a research project in which the risk of harm is considered to be unacceptable.
20. See Note 16.
21. A signed consent is obtained whenever possible, and is obtained in all projects involving a greater than minimal level of risk (see Note 19.). However, in some research projects, obtaining a signed consent is very difficult and perhaps impossible. This may be the case where the nature of the data to be collected is sensitive, context dependent, and/or involves responses about people other than the subject (respondent) (e.g., reactions to stress or opinions about leadership). This may also be the case where the data are to be collected from a vast number of subjects by methods such as interviews or questionnaires delivered by mail or over the phone or the Internet. When collecting sensitive data is the issue, then having to sign a consent form might prevent individuals from participating because of fear that the confidentiality of their data will be jeopardized in spite of any safeguards to confidentiality that the investigators might promise. For unsigned consent, a covering letter or password-protected electronic form must be sent to the subjects, indicating such matters as the purpose of the research project, that participation is voluntary, that risk is minimal, how data will be used, that consent is obtained by retuning the data collection survey, etc.
22. Naturalistic observations refer to the study of behaviour in a natural environment. Normally, naturalistic observations are considered to be of minimal risk (see Note 19.).
23. Direct experiments are those in which human subjects are subjected to a physical, physiological or psychological stress. Indirect experiments, including naturalistic observations (see Note 22.), are those where human subjects are not directly exposed to a stressful environment; rather, data collection normally is limited to such techniques as surveys (personal or other) by telephone, e-mail or other means, or by personal interview.